Attorney Docket No. 15021-6

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	)	
	)	
Christopher A. Starr and Todd Zankel	)	
	)	Group No.: **1657**
Serial No. **10/501,028**	)	
	)	Examiner: **Kailash C. Srivastava**
	)	
I.A. Filing Date: **January 10, 2003**	)	
	)	
For: **Use of p97 as an Enzyme Delivery Of Therapeutic Lysosomal Enzymes**	)	

The Commissioner of Patents
& Trademarks
Washington, D.C. 20231
U.S.A.

Dear Sir:

DECLARATION UNDER 37 CFR §1.132

I, Wilfred A. Jefferies, a citizen of Canada, and resident of South Surrey, British Columbia declare that the following facts are within my knowledge and are true.

1. I reside at 12596 23rd Avenue, South Surrey, British Columbia, Canada.

2. I am currently a Professor at the University of British Columbia in the Michael Smith Laboratory.

3. I have been conducting research in the field of Immunology since 1981. I have authored over 70 publications which have been published in refereed journals including Nature. I am an inventor on 5 issued or pending United States Patents. I have worked with p97/melanotransferrin for over 13 years and have

patents related thereto. My curriculum vitae is attached to this Declaration as Exhibit A.

4. I have read U.S. Patent Application Serial No. 10/501,028 filed January 10, 2003 (hereinafter "the Application") and understood the disclosure and the claims of the Application.

5. I have read and understood the office action that issued on the Application on October 29, 2008. In particular, I note the Examiner's objection to the specification as not being enabling for a method to treat a subject having a lysosomal storage disease comprising a method wherein a composition comprising a p97 molecule covalently linked to a protein is actually administered to said subject/patient. I respectfully disagree with the objection.

6. For the treatment of lysosomal storage diseases, the first step is to refit the lysosomal enzyme, either chemically or genetically, with carrier sequences that specify transport from blood to brain and into the lysosome of cells. There are at least four requirements necessary as shown in the figure attached as Exhibit B to this Declaration:

a. the carrier moiety must be efficiently transcytosed across the brain capillary endothelium and into the interstitial fluid of the brain. This ability must remain unimpeded within the context of an association with the lysosomal enzyme.

b. as the complex appears in the interstitial fluid, affected brain cells must be able to take it up. Expression of receptors can be quite tissue specific so there is no reason to assume that the same receptors involved in transcytosis will be adequately represented on a majority of cells in the brain.

c. the carrier should specify, or at least not interfere with, the lysosomal routing of the enzyme after uptake.

d. the carrier should not interfere with the action of the enzyme on its natural substrate nor should it significantly reduce the lysosomal half-life of the enzyme.

7. In order to demonstrate that p97 conjugated to a lysosomal enzyme can be delivered to a lysosome in a cell, experiments have been conducted under my general supervision. Details of the experimental results are discussed below.

In vitro blood brain barrier model

8. It was demonstrated that p97 is transcytosed in an in vitro blood brain model shown in Exhibit C to this Declaration. The model consists of a co-culture of a monolayer of bovine brain capillary endothelial cells and a monolayer of newborn rat astrocytes separated by a porous filter. Factors secreted by the astrocytes induce the formation of tight junctions between the endothelial cells. The quality of the monolayer is determined by measuring electrical resistance between the upper and lower chambers or the permeability of vascular space markers such as sucrose. Assuming a tight monolayer, transfer of a protein from the apical to the basolateral chamber is an indication that transcytosis has occurred. Results, shown in Exhibit D to this Declaration, show the appearance of p97 in basolateral chamber over time after spiking the protein into the apical chamber. This phenomena was found to be temperature sensitive and saturable. P97 did not change the permeability of the barrier to sucrose and p97 was transferred between the chambers intact.

In situ Mouse Brain Perfusion Model

9. It was also demonstrated that the volume of distribution of p97 into parenchyma was found to be 10 times that of the cerebrovascular space marker inulin as shown in Exhibit E to this Declaration. Thus, p97 is transcytosed across brain capillary endothelial cells.

P97-iduronidase Fusions

10. Fusions of p97 and iduronidase were generated as shown in Exhibits F and G to this Declaration. The fusions to date have consisted of N-terminal p97 or fragments of p97 linked to C-terminal iduronidase through a short linker. Fusions are expressed transiently in 293 cells. All fusions are expressed and secreted to at least the same extent as iduronidase alone. Assessment of fusion specific activity with the monosaccharide substrate reveals that it is about half that of iduronidase alone. This is about the theoretical number if no diminution of iduronidase activity in the fusion is assumed. Phosphorylation state can also play a role in determining tissue distribution. Absence of phosphate would be expected to benefit brain delivery by handicapping Mannose Phosphate Receptor (MPR) mediated uptake into non-CNS tissue. No detectable mannose-6-phosphate was found on the fusions prepared as shown in Exhibit H to this Declaration.

Lysosomal Localization

11. To determine whether p97 is taken up by neuronal cells, the following experiment was performed. Colocalization of endocytosed fluorescently-labeled iduronidase and fluorescently-labeled p97 in a neuronal cell line was noted, indicative of uptake and lysosomal localization. In this experiment, fluorescently-labeled p97 and fluorescently-labeled iduronidase as a positive control were incubated with HCN-2 neuronal cells and the distribution of the proteins determined after two hours by fluorescence microscopy. Both proteins were taken up and both showed a punctate staining pattern characteristic of lysosomal localization as shown in Exhibit I to this Declaration.

Release of enzyme in lysosome

12. It was also found that p97 can be removed upon incubation of the fusions with cathepsin D. Digesting away the p97 leaves iduronidase intact as shown in Exhibit J to this Declaration.

13. The above experiments demonstrate that p97 conjugated to a lysosomal storage enzyme, iduronidase, can be transported across the BBB into the lysosome where the p97 can be digested releasing the active enzyme.

14. In view of all of the above, I believe that the claims as currently on file in the application are sufficiently enabled under 35 USC §112, first paragraph.

15. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statement and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardize the validity of the Application or patent resulting therefrom.

APR 2 7 2009

DATE

Wilfred A. Jefferies

Exhibit A

THE UNIVERSITY OF BRITISH COLUMBIA
Curriculum Vitae for Faculty Members

Date: April 23, 2009 **Initials:** WAJ

1. **SURNAME:** JEFFERIES **FIRST NAME:** Wilfred
MIDDLE NAME(S): Arthur

2. **DEPARTMENT/SCHOOL:** Michael Smith Laboratories, Biomedical Research Centre, Medical Genetics, Microbiology and Immunology, and Zoology

3. **FACULTY:** Science, Medicine

4. **PRESENT RANK:** Professor **SINCE:** March 8, 1999

5. POST-SECONDARY EDUCATION

University or Institution	Degree	Subject Area	Dates
University of Victoria	B.Sc.	Biochemistry (First Class with Distinction)	1981
University of Oxford	D. Phil. (Oxon)	Molecular Immunology	1985

6. EMPLOYMENT RECORD

(a) Prior to coming to UBC

University, Company or Organization	Rank or Title	Dates
University of Victoria Department of Biochemistry and Microbiology	Undergraduate Research Assistant	1979
B.C. Cancer Control Agency, University of British Columbia, Terry Fox Lab	Undergraduate Research Project	1980
University of British Columbia Department of Pediatrics	Work-Studies Student	1981
Institut Suisse de Recherches Expérimentales sur le Cancer Lausanne, Suisse	Postdoctoral Research Fellow	1985-1987
Ludwig Institute for Cancer Research, Karolinska Institute, Stockholm, Sweden	Postdoctoral Research Fellow	1987-1989

(b) At UBC

University, Company or Organization	Rank or Title	Dates
University of British Columbia	Assistant Professor	1989-1994
University of British Columbia	Associate Professor	1994-1999
University of British Columbia	Professor	1999-present

(c) **Date of granting of tenure at U.B.C.: July 1, 1994**

7. LEAVES OF ABSENCE

No leaves taken.

8. TEACHING

(a) Areas of special interest and accomplishments

(b) Courses Taught at UBC

Session	Course Number	Scheduled Hours	Class Size	Hours Taught			
				Lectures	Tutorials	Labs	Other
1989-90	MICRO 530	36	12	6			
	BIOL 350	36	150	2			
	BIOL 437		2			>100	Research
	BIOL 448		2			"	projects
	BIOL 449		1			"	
1990-91	MICRO 430	36	20	6		>100	Research
	BIOL 437		2				projects
90-91	MICRO 200	72	100	15			
(summer)	BIOL 448		2			"	
	MICRO402/ MED GEN 410	36	40	13 20			
	MICRO 302	36	150	20			
	PHARMAC 521	36	15	1			
1991-92	BIOL 437		2			>100	Research
	BIOL 448		2			"	projects
	MICRO 200	72	275	13			
	MICRO 402/ MED GEN 410 (Course Organizer)	36	100	13			
1992-93	MICRO 200	72	275	13			
	MICRO 530	36	12	6			
	BIOL 437		2			>100	Research
	BIOL 448		2			"	projects
	MICRO 402/ MED GEN 410 (Course Organizer)		100	13			

Session	Course Number	Scheduled Hours	Class Size	Hours Taught			
				Lectures	Tutorials	Labs	Other
1994-95	BIOL 437 BIOL 448 MICRO 200 MICRO 402/ MED GEN 410 (Course Organizer)	 72 36	2 2 275 100	 13 13	 	>100 " 	Research Projects
1995-96	BIOL 448 MICRO 202 MICRO 402/ MED GEN 410 (Course Organizer)	 36 36	3 275 70	 15 13	 1 	>100 	Research Projects
1996-97	BIOL 448 MICRO 202 MICRO 402/ MED GEN 410 (Course Organizer)	 36 36	3 275 70	 15 13	 1 	>100 	Research Projects
1997-98	BIOL 448 MICRO 202 - Section 1 Section 3 MICRO 402/ MED GEN 410 (Course Organizer)	 36 36 36	3 275 275 70	 12 12 13	 1 1 	>100 	Research Projects
1998-99	MICRO 530 MICRO 202 MICRO 402	36	12	6			
1999-2000	MICRO 202 MICRO 402 MED GEN 410 MICB 430 MICB 530	36 36 36 36 36					
2000-2001	MED GEN 410 MICRO 430 MICRO 530 MICRO 449	36 36 36	10 10 10 2	16 25 16			 Research Projects

Session	Course Number	Scheduled Hours	Class Size	Hours Taught			
				Lectures	Tutorial	Labs	Other
2001-2002	MICRO 530	15	16	5			
	MICRO 430	16	25	4			
	MED GEN 520	16	16	8			
	MICRO 449		2			>100	Research
2002-2003	MICRO 202	15	16	5			
	MICRO 430	15	16	8			
	MICRO 449		1			>100	Research
2003-2004	MICRO 202	15	16	5			
	MICRO 430	15	16	8			
	MICRO 449	1	1			>100	Research
2004-2005	MICRO 402	30	75	26			
	MICRO 449		2			>100	Research
2005-2006	MICRO 402	18	78	12			
	MICRO 449		1			>100	Research
2006-2007	MICRO 402	18	72	12			
	MICRO 449		1			>100	Research
2007-2008	MICRO 402	18	72	12			
2008-2009	MICRO 402	18	76	12			
	MICRO 449		2			>100	Research

1. Graduate Students Supervised

Name of Trainee	Program Type *	Dates		Degree	Year Degree Received	Current position and Institution
		From	To			
Haidl, Ian	PhD -MI	1989	1996	PhD	96	Assistant Professor, Dalhousie NS
Reid, Gregor	PhD -Z	1989	1996	PhD	96	Staff Scientist, Children's Hospital of Philadelphia
Lomas, Cyprien	PhD -Z	1989	1999	PhD	99	Director of the Learning Centre, Land & Food Systems, UBC
Lippe, Roger	PhD -Z	1990	1995	PhD	95	Associate Professor at University of Montreal
Food, Mike	MSc.-MI	1990	1993	M.Sc.	93	Entrepreneur
Yang, Joseph	MSc. -Z	1993	1999	M.Sc.	99	Lawyer with Farris, Vaughn, Wills & Murphy LLP, Vancouver
Alimonti, Judie	PhD -Z	1994	1998	Ph.D.	98	Staff Scientist CDC, Winnipeg
Tiong, Jacqueline	PhD -MI	1994	2001	Ph.D.	01	Director of Corporate Development, Allon Therapeutics, Vancouver
Moise, Alex	PhD -Z	1994	2000	Ph.D.	00	Instructor, Case Western Reserve University, Cleveland
Lizee, Greg	PhD -Z	1993	2000	Ph.D.	00	Assistant Professor, U. Texas, MD Anderson Cancer Center, Houston
Hsu, Forrest	MSc -Z	1995	1997	M.Sc.	97	Medical Doctor (UBC)
Bromm, Michael	MSc-Z	1995	1998	B.Sc.	98	Lawyer, Associate with Lang Michener LLP, Vancouver
Walker, Brandie	PhD -MI	1995	2002	Ph.D.	02	Medical Doctor (U. Calgary)
Kotturi, Maya	PhD -MI	1998	2004	Ph.D.	04	Staff Scientist, La Jolla Institute for Allergy & Immunology, CA
Dickstein, Dara	PhD-MG	1998	2004	Ph.D.	04	Assistant Professor, Mt. Sinai Medical Center, Dept Neuroscience, N.Y.
Grant, Jason	PhD -MI	1999	2005	Ph.D.	05	Post-Doctoral Fellow, U. Alberta
Chen, Susan	MSc -Z	2000	2006	—	—	Alternative Medicine Practitioner - Traditional Chinese Medicine
Johnson,Laura	PhD -Z	2000	2004	Ph.D.	05	Assistant Professor, NIH
Biron, Kaan	PhD -MI	2002	Present			Graduate Student, UBC
Tian, Mei Mei	PhD -MI	2002	Present			Graduate Student, UBC
Wilcox, Sara	PhD -MI	2002	Present			Graduate Student, UBC

Seipp, Robyn	PhD -Z	2002	2008	Ph.D.	08	Postdoctoral Fellow, CDRD Vancouver
Setiadi, A. Francesca	PhD -Z	2002	2007	Ph.D.	07	Post-doctoral Fellow, Stanford CA
Omilusik, Kyla	PhD -MI	2003	Present			Graduate Student, UBC
Young, Joanne	PhD -Z	2003	Present			Graduate Student, UBC
Wang, Teresa	MSc -MI	2005	Present			Graduate Student, UBC (on business training leave)
Garduno, Alonso	MSc -MI	2005	2007	—	—	Medical School, Mexico City
Hartikainen, Jennifer	PhD -MI	2006	Present			Graduate Student, UBC

* Z = Zoology
MI = Microbiology & Immunology
MG = Medical Genetics

Post-doctoral Fellows Supervised

1991-1992 Jonas Ekstrand (Swedish Research Council Fellowship)
1991-1992 Sylvia Rothenberger (Swiss National Research Foundation)
1994-1996 Catherine Barbey (Swiss National Research Foundation)
1995-1997 Iku Moroo (Chiba University Graduate School of Medicine)
1999-2003 Cheryl Pfeifer (MRC/CIHR Operating Grant)
1999-2004 Maki Ujiie (Human Frontier Program Post-Doctoral Fellowship)
2004-2006 Ya Ke (Hong Kong Polytechnic Fellowship)
2004-2008 Anna Reinicke (CIHR Fellowship in Transplantation)

Research Associates

1991-1998 Reinhard Gabathuler (Tobacco Research Council)
1993-1994 Chris Nicol (Synapse Technologies)
1995-1998 Malcolm Kennard (Synapse Technologies)
1999-2003 Qian-Jin Zhang (GeneMax Pharmaceutical CRA)
1999-2007 Genc Basha (MRC/CIHR Operating Grant)
2001-2005 Yuanmei Lou (GeneMax Pharmaceutical CRA)
2002-2006 Tim Vitalis (TapImmune Pharmaceutical CRA; CIHR Operating Grant)
2004-present Cheryl Pfeifer

• Continuing Education Activities

•Visiting Lecturer (indicate university/organization and dates)

1. Simon Hunt, PhD, Sabbatical Visitor (University of Oxford, U.K.), 1996
2. Iku Moroo, Chiba University School of Medicine, Chiba, Japan, 1997-98
3. Simon Hunt, PhD, Visiting Scientist (University of Oxford, U.K.), 2007
4. Stephen McQuaid, Visiting Scientist (Queen's University, Belfast, Ireland), 2008

Other

Thesis Committee member for: (26)	**Supervisor**
Bruce Banfield; Peter Cheung	Frank Tufaro
Kathy Horley; Andrew Pyszniuk	Fumio Takei
Clay Welder, Andrea Ingram, Carmine Carpenito, Mary Gilbert	Don Moerman
Richard Hegele	Jim Hogg
William Craig	Connie Eaves/Peter Lansdorp
Stephen Land	Peter Hochachka
David Hunt	Julia Levy
Chris Fraser	Keith Humphries
Patrick Rebstein	Gerry Weeks
Arpeta Matia	Pauline Johnson
Bevan Voth, Jaime Bellatin	Rob McMaster
Amanda Jones	Hermann Ziltener
Bevan Voth, Jaime Bellatin	Rob McMaster
Amanda Jones	Hermann Ziltener
Jose Rey-Ladino	Niel Reiner
John Chiu	Alan Eaves
Madelaine Lemieux	Connie Eaves
Kelly Brown	Pauline Johnson
Julia Boyle	Hung-Sia Teh
Jennifer Cross	Pauline Johnson
Mark Bleakley	Ross MacGillivray
Ann Wong	Ross MacGillivray

Dissertation Committee member for: (19)	
Chris Fraser, Ph.D.	Keith Humphries
Mark Daly, MSc.	Hugh Brock
Carmine Carpenito, MSc	Fumio Takei
Peter Cheung, MSc.	Frank Tufaro
Mike Food, M.Sc.	Wilfred Jefferies
Clay Welder, M.Sc.	Fumio Takei
Richard Hegele, Ph. D.	Jim Hogg
William Craig, M.Sc.	Connie Eaves/Peter Lansdorp
Helena Chaye, Ph.D.	Shirley Gillam
Brad Spiller, Ph. D.	Dana Devine
Mary MacDonald Ph.D.	W. Rob McMaster
Charlotte Morrison Ph.D.	W. Rob McMaster
Andrew Pyszniuk Ph.D.	Fumio Takei
Arpita Maiti	Pauline Johnson
Angus Murray	W. Rob McMaster
HB Choi	James McLarnon
Jae Kyu Ryu	James McLarnon
Klaus Gossen	Hermann Ziltener
David Hudson	Ross MacGillivray

External examiner: (2)	
Mark Luscher Ph. D. Toronto	Brian Barber

2. SCHOLARLY AND PROFESSIONAL ACTIVITIES

(a) Areas of special interest and accomplishments

I have a longstanding interest in the mechanisms of induction of immune responses. I was a pioneer in the identification a molecular mechanism by which cancer cells evade destruction by the host immune response. This was a significant discovery that still reverberates as a seminal finding in the field. It has spawned no less than 200 research papers from other cancer researchers and provides a clear path towards developing new treatment for metastatic cancers. I have used these findings to develop completely novel immunological approaches to eradicate tumors. These approaches are a departure from other therapeutic modalities because they provide a bridge between the fields of vaccines and gene therapy, and provide a generalized immunotherapeutic approach for cancers of various types. In addition, his findings have provided prognostic indicators of cancer progression. These findings have been widely hailed to be of fundamental importance for understanding and treating cancers of many kinds. This translational research now forms a basis for generalized cancer therapy that has moved from the bench forward into clinical trials.

I have authored some of the most widely read and downloaded papers in recent immunological history. These include the identification of the process whereby dendritic cells trigger primary immune responses against foreign pathogens and cancer cells. These studies, first published in Nature Immunology, were amongst the most read research papers for all of Biology in that year and remains a hugely cited finding in Immunology that has revised the pages of many Immunology text. In addition, our recent studies published in PLoS Pathogen, have identified a new method for enhancing and extending the vaccine supply against many foreign pathogens. These studies appear to provide a solution to a tremendous societal problem of meeting the needs for vaccine supplies in the face of emerging pandemics. The profound nature of these contributions to healthcare should be recognized.

Earlier in my career at Oxford University, I was also interested in the role of iron in promoting cancer cell growth and was the first to define a pathway of iron acquisition by melanomas. These discoveries lead directly to methods of removing cancer cells from autologous bone marrow: a technology that is still in use today. Furthermore, I was instrumental in defining the receptor system for the passage of iron from the blood into the brain. This seminal discovery has lead to the development of new drug delivery systems for the delivery of anti-cancer drugs into the brain for the treatment of brain tumors. This research has provided the impetus for the creation of an entirely new area of drug development used for the treatment of other diseases of the brain, including lysosomal storage diseases such as Tay-Sachs and Sandhoff disease. These studies are widely cited and have had an immense impact on understanding the biology of the blood brain barrier. My continued interest in iron transport to the brain, led to making the discovery of the first unique marker of reactive microglia associated with the senile plaques in Alzheimer's disease brains. This remains the first and only marker of its kind. We then demonstrated that the marker molecule, called p97, is elevated in the blood and cerebral spinal fluid of individuals with Alzheimer's disease. Subsequent, clinical trials demonstrated that this molecule is the first stand-alone serum protein marker for this disease.

As a result of my interest in the Blood-Brain Barrier, my group recently demonstrated that this barrier is impaired in Alzheimer's disease prior to disease onset and the appearance of plaques in the brain. These pioneering studies have again created the seed for another new area of scientific investigation

that is being actively followed up by the research community. This finding links Alzheimer's disease and stroke in a unique way and may form the basis to molecularly understand modality of AD vaccines and methods to treat the disease.

Quality of publications: Many of my scientific papers are published in the world's most outstanding scientific journals including Nature, PNAS, Nature Immunology, Journal of Experimental Medicine, EMBO Journal, Nature Biotechnology, FASEB Journal, Journal of Biological Chemistry, Nature Biotechnology, PLoS Pathogens and in many cancer related journals, including the Cancer Research and the International Journal of Cancer Research. In addition, I have published several reviews in the prestigious Trends Journals and am the author of innumerable conference proceedings.

Presentations: I am internationally recognized as a scientific leader and innovator, and continue to present my breakthroughs as an invited speaker to Gordon conferences and to Keystone Meetings as well as many international congresses. My impact on the scientific awareness of the general public through my breakthroughs in cancer research can be gauged by the large number of publications that have reviewed these discoveries. These include popular journals such as Readers Digest, Popular Mechanic and newspapers such as the New York Times, the London Telegraph, the Washington Post and the Globe and Mail, just to name a few.

Record of grant funding: I have an outstanding record of peer reviewed grant funding. I currently hold two CIHR grants, a Western Economic Diversification grant, and a Multiple Sclerosis Research grant. Other grants I have held include the Sanfilippo Chilldren's Research Foundation, Genome Canada, Prostate Cancer Research Foundation of Canada, the NIH, NSERC, CANVAC, CANFAR, and NCIC.

Mentorship: I have an outstanding record as a mentor of graduate students. I have supervised 28 graduate students, 19 of which have graduated so far during my tenure at UBC. Many of these students now hold independent professorships at Universities throughout the globe.

Impact of infrastructure at University: As Director of the UBC Life Sciences Centre Transgenic Facility, I participated in the writing and presenting UBC CFI award entitled "Centre for Disease Modeling", and I have been a driving force in developing novel transgenic techniques that should allow the investigation of new models of human diseases such as cancer. The CFI award will allow completion and extensive infrastructure for the UBC Life Sciences Centre Animal Care facility, and the Genome Canada Award will provide operating funds for state-of-the-art research at UBC. I was a co-investigator on the successful Genome Canada award, "North American Conditional Mouse Mutagenesis Project", with total funding of over $8 million between three Genome Centres across Canada. I spent a significant amount of my time serving as the Director of three separate animal facilities at UBC, including: the Small Mammal Unit at Zoology South Campus, the UBC Transgenic Animal Facility and the UBC Rederivation Facility. The latter two facilities have provided state of the art animal technologies to the greater biotechnology and university community. I have spent literally hundreds of hours, directing, organizing and writing grants to fund these animal facilities at UBC for the entire University community. I have also been involved in leading a new group called TransArc Network that is a collaboration between UBC, UNBC, CMMT, UVic, SFU and BCCRA to coordinate all transgenic research animal services across the province. During this year we were able to raise 1.4 Million Dollars from Western Diversification for a new Pan-B.C. Animal Services Network. The first of its kind in the world where mutlicentre animal facilities will unite the services they provide individually into a single point of entry animal service provider. This will now be the network that will provide transgenic and toxicology animal services to the whole community. Furthermore, this network will grow by added

additional capablitlities such as P3 research capacity for researchers across B.C. I was also instrumental as Director of the Rederivation Facility at UBC in planning and commencing of a new multi-million dollar Animal Rederivation Facility building on campus, that I will direct.

Recognition: I have received recognition as the recipient of a University Killam Faculty Research Fellowship and has received numerous other fellowships and scholarships throughout my career. I have also been awarded the Microcirculatory Society's Wiederhelm Award in 2008, for most cited article between 2003-2007: "Blood-brain barrier permeability precedes senile plaque formation in an Alzheimer disease model" (in Microcirculation).

Commercialization and out-licensing: I hold no less than 20 issued patents that cover many of my discovered. These international patents form the core technology foundations of four biotechnology and pharmaceutical companies that have employed dozens of individuals over the past 15 years in the development of my discoveries.

(b) Research or equivalent grants (indicate under COMP whether grants were obtained competitively (C) or non-competitively (NC))

Granting Agency	Subject	COMP	$ per year	Year	Principal Investigator	Co-Investi-gator(s)
National Cancer Institute of Canada	Molecular studies on the transport, recognition and inhibition of MHC Class I gene products	C	45,088 47,539 61,000	89-90 90-91 91-94	Jefferies	
National Cancer Institute of Canada	**Equipment** for above	C	36,610	89-91	Jefferies	
National Cancer Institute of Canada	Molecular studies on the transport, recognition and inhibition of MHC Class I gene products and characterization of the melanoma-associated protein, melanotransferrin	C	63,025 59,749 60,934	91-92 92-93 93-94	Jefferies	
National Cancer Institute of Canada	Viral and genetic mechanisms which lower MHC Class I cell surface expression	C	103,000	94-97	Jefferies	
British Columbia Health Research Foundation	The role of the E3/19k protein of Adenovirus-2 in lowering the cell surface	C	45,000 50,000	89-90 90-	Jefferies	

	expression of HLA molecules and in viral persistence			91		
British Columbia Health Research Foundation	The function of the melanoma associated protein melanotransferrin	C	27,000	92-94	Jefferies	
British Columbia Health Research Foundation	**Equipment** for Molecular action of cyclosporin A	C	14,000	89-90	Jefferies	
British Columbia Health Research Foundation Emergency	**Equipment** – Cryopreservation unit	C	5,000	91-92	Jefferies	
Natural Science and Engineering Council of Canada – UBC	**Equipment** for The generation of antigen presenting mutants	C	25,000	1990	Jefferies	
Natural Science and Engineering Council of Canada	**Equipment** – Cryopreservation unit	C	8,000	90-91	Jefferies	
American Council for Tobacco Research	The role of the E3/19k protein of Adenovirus-2 in lowering the cell surface expression of HLA molecules and in viral persistence	C	91,000 101,000 112,000 60,000 88,400 91,000	91 92 93 94 95 96	Jefferies	
Vancouver Foundation/Medical Services Association	An early detection test for Alzheimer's disease	C	45,000	91-93	Jefferies	
Medical Research Council of Canada	Human melanotransferrin	C	74,000	93-97	Jefferies	
Medical Research Council of Canada	Molecular characterization of antigen processing variants	C	60,000	93-97	Jefferies	
B.C. Science Council	An early detection test for Alzheimer's disease	C	45,000 104,000	95-96 97-98	Jefferies	
National Centre of Excellence for	Transport across the Blood Brain Barrier	C	48,000	93-98	Jefferies	

Neural Regeneration						
Medical Research Council of Canada	Characterisation of the function of Melanotransferrin	C	52,673	97-00	Jefferies	
Medical Research Council of Canada	Antigen Processing in the Context of MHC Class I molecules	C	94,359	97-00	Jefferies	
Natural Science and Engineering Research Council of Canada	Novel eukaryotic expression Systems	C	108,760	97-00	Jefferies	
National Cancer Institute of Canada	Animal models of adenovirus persistence	C	25,356	97-98	Jefferies	
National Cancer Institute of Canada	Studies on the structure and function of MHC Class I molecules	C	25,356	97-98	Jefferies	
National Cancer Institute of Canada	Studies on exogenous pathway of antigen presentation	C	111,000	99-02	Jefferies	
NSERC	Novel recombinant protein production system based on expressing GPI-anchored proteins in Dictyostelium discoideum	C	108,760	97-00	Jefferies	
CANVAC	Enhancing efficiency of antigen presentation using TAP based immunotherapy	C	28,050	00-02	Jefferies	
Canadian Institute of Health Research	Studies on antigen processing in the context of MHC class I molecules	C	126,028	00-04	Jefferies	
National Cancer Institute of Canada	Maintenance of calcium ion homeostasis , a new viral immuno-evasion mechanism	C	118,990	01-04	Jefferies	
BCRP Concept Award: U.S. Army Medical Research Acquisition Activity	Novel Immunotherapy for Malignant Breast Carcinomas		50,000US	01-02	Jefferies	
CANFAR	Identification of cellular interaction of MHC I cytoplasmic domain	C	80,000	01-02	Jefferies	

	displayed by HIV nef.					
Canadian Institute of Health Research	The role of p97 and a novel transferrin receptor homologue in metal uptake	C	124,065	01-06	Jefferies	
Canadian Institute of Health Research	Delivery of therapeutic proteins across the blood-brain barrier	C	59,000	04-06	Jefferies	
Canadian Institute of Health Research	Studies on antigen processing in the context of MHC class I molecules	C	131,070	04-08	Jefferies	
Canadian Institute of Health Research	Aspects of antigen presentation by breast and lung carcinomas and dendritic cells	C	104,133	05-08	Jefferies	
Western Economic Diversification	Support for the Rederivation Facility	C	52060	04-08	Jefferies	
Canadian Foundation for Innovation	UBC Centre for Disease Modeling	C	125,117	04-09	Teh	Jefferies, Hancock, Jean, Brunham, Finlay, Lefebvre, McNagny, Brooks,Kieffer
Canadian Institute of Health Research	Research Resource Equipment Grant - Determinants of genome stability	C	$125,325	05	Phil Hieter	Finlay, Foster, **Jefferies**, Kronstad, Measday, Snutch
Sanfilippo Children's Research Foundation	Development of a therapeutic tool for the delivery of proteins across the blood-brain barrier	C	$80,000	06-08	"	
Genome Canada	NorCOMM: North American Conditional Mouse Mutagenesis Project	C	2,000,000	06-07	Geoff Hicks/Janet Roussant	**Jefferies**, Stanford, Wurst, Bradley, Skarnes, Ding, Rancourt, Nagy, Hughes, Hoodless, Marra, Roder, Gondo, Lefebvre, MacVicar, Hannon, McKerlie, Lloyd, Einsiedel
Canadian Prostate Cancer Research Foundation	Regulators of prostate cancer immunogenicity	C	$60,000	06-07	Jefferies	
Michael Smith	BC Mouse Models Platform	C	$50,000	06	Jefferies	Payne, Leavitt

Foundation for Health Research	- Technology/Methodology Platform Award for LOI					
Multiple Sclerosis Society of Canada	Pilot Project Award	C	$35,000	08	Jefferies	McQuaid
Canadian Institute of Health Research	Studies on antigen presentation in dendritic cells	C	$140,000	08-13	Jefferies	
Western Economic Diversification	BC Pre-Clinical Research Consortium	C	1,500,000	08-10	Harvey-Clark	Jefferies, Bally
Canadian Prostate Cancer Research Foundation	Regulation of antigen processing machinery in prostate carcinomas	C	$60,000	08-09	Jefferies	
Canadian Institute of Health Research	Dissecting the molecular mechanism of HIV nef immunosubversion	C	100,000	08-09	Jefferies	
Canadian Institute of Health Research	Studies on p97 (Melanotransferrin)	C	100,000	09-10	Jefferies	
Canadian Stroke Network/ CIHR	Vascular Pathology in Models of Alzheimer's Disease	C	100,000	09-10	Jefferies	

(c) Research or equivalent contracts (indicate under COMP whether grants were obtained competitively © or non-competitively (NC).

Contract Agency	**Subject**	**COMP**	**$ per year**	**Year**	**Principal Investigator**	**Co-Investigator(s)**
Synapse Technologies Inc	AD diagnostics	C	$125,000	96-02	Jefferies	
GeneMax Inc	Novel immunotherapy for malignant carcinomas	N	$125,000	00-05	Jefferies	
GeneMax Inc	TAP Vaccines	N	$147,348	05-06	Jefferies	
INEX	To Determine Biodistribution of siRNA using Fluorescent Microscopy Techniques	N	$24,000	07	Jefferies	

(d) Invited Presentations

1. 1997 Molecular Biology of Alzheimer's Disease, IBC Conference San Francisco, California, p97 and Alzheimer's Disease
2. 1998 Round Table discussion on Biomarkers of Alzheimer's Disease International Congress of Alzheimer's and related diseases, Amsterdam
3. 1998 Toward a Comprehensive Theory for Alzheimer's Disease Orlando Florida, AD Association
4. 2002 Gordon Conference, Barriers of the Central Nervous System. New Hampshire, USA.
5. 2002 Annual Canadian Vaccine Meeting. Toronto, Ont., Canada.

6. 2002 Progress in Vaccination against Cancer (PIVAC). British Society for Immunology. Nottingham, England.
7. 2003 Keystone Conference – Tumor Immunology Keystone, Colorado
8. 2005 Keystone Conference – Tumor Immunology II. Keystone, CO
9. 2006 9th International Symposium on Dendritic Cell - Edinburgh, Scotland (delivered by graduate student Robyn Seipp)
10. 2006 Vaccines on the Horizon - 7th Canadian Immunization Conference, Winnipeg, MB
11. 2007 Prostate Cancer Research Retreat, Canadian Prostate Cancer Research Foundation, Oakley, ON (delivered by graduate student Francesca Setiadi).
12. 2007 Vaccine Evaluation Centre, Vancouver, BC April 2007
13. 2007 Keystone Conference – Cancer Vaccines. Banff, AB March/April 2007
14. 2007 Cerebral Vascular Biology Conference, Ottawa, ON June 2007
15. 2007 Gordon Conference, Antigen Cross-Presentation, Big Sky Montana, Sept 2-7, 2007
16. 2008 University of British Columbia, Establishment of TransARC Network, Vancouver, BC Sept. 2008

(e) Other Presentations

1. 1996-1997 Newspaper interviews
2. Outreach presentations to elementary schools – "Jurassic School"
3. CBC Radio interview
4. 2002 Popular Mechanics
5. 2002 Vancouver Courier
6. 2002 BTV, Business Television
7. 2003, Vancouver Sun
8. 2003, Ubyssey
9. 2004, Vancouver Sun
10. 2004, CBC Radio
11. 2005, BC Cancer Agency, Victoria BC
12. 2006, SHI Consulting interview for NorCOMM
13. BioSpace Beat: GeneMax Corp. (Formerly Eduverse.Com)'s (GMXX) TAP-1 Technology Corroborated In Models Of Skin Cancer http://www.biospace.com/news_story.aspx?StoryID=16079120&full=1
14. Vancouver Sun: Canwest News Service, byline by Pamela Fayerman: "Less vaccine needed: Study", Jan 26, 2006
15. Vancouver Sun: Front Page: Canwest News Service, byline by Pamela Fayerman: "UBC researchers make pandemic flu vaccines safer, more effective: Vaccine effective at 1% of normal dose after immune-system booster added", Jan 26, 2006
16. Victoria Times Colonist: Canwest News Service, byline by Pamela Fayerman: "Researchers harness genes to create new vaccines", Jan 26 ,2006
17. Montreal Gazette: Canwest News Service, byline by Pamela Fayerman: "Profs give boost to vaccines: An added immune system gene makes lower doses more effective, study finds", Jan 26, 2006
18. Edmonton Journal: Canwest News Service, byline by Pamela Fayerman: "Low-dose vaccines work in tests: Stockpiles would last longer in pandemic", Jan 26, 2006
19. Calgary Herald: Canwest News Service, byline by Pamela Fayerman: "Scientists develop low-dose vaccines", Jan 26, 2006
20. http://strategis.ic.gc.ca/epic/site/p-pp.nsf/en/ph01656e.html "Diagnostics and Therapeutics UpdatePublication that Pinpoints TAP Defect in Metastatic Carcinomas" August 25, 2005

21. UBC Reports, Dec 4, 2004, Vol. 49, No. 12 "In the News" Compiles by Brian Lin.
22. Calgary Herald: Canwest News Service, byline by Chad Skelton: "Alzheimer's find may allow early treatment: Warning sign discovered in mice", March 4, 2004
23. Edmonton Journal: Canwest News Service, byline by Chad Skelton: "Early sign of Alzheimer's reported: Patients could be treated decades sooner, UBC researchers say", March 4, 2004
24. Victoria Times Colonist: Canwest News Service, byline by Chad Skelton: "Research points to early warning of Alzheimer's", March 4, 2004
25. Vancouver Sun newspaper : Front Page: Canwest News Service, byline by Chad Skelton: "Signs of disease could start in early 20s: UBC discovery creates hope for early Alzheimer's treatment", March 4, 2004
26. Northern Daily News (Kirkland Lake): Canwest News Service, byline by Chad Skelton: "Alzheimer's warning may soon be reality", March 4, 2004
27. 2006 Weather Channel program on vaccines breakthrough
28. CIHR Highlights of Vaccine Study Impact 2005
29. Prostate Cancer Research Association News 2006
30. NATURE Medicine, 2006, Vol. 12, No. 2, pg 173. Research Highlights: "Transport genes speed vaccines".
31. UK Daily Mail, November 2007: Cancer cells hide from immune system with invisibility cloak
32. ScienceDaily: Nov 10, 2007: 'Instruction Manual' That Tells Cancers How To Hide From Immune System Discovered (www.sciencedaily.com)

(f) Other

Coordinated University Grants:

Title of Grant: BC Pre-Clinical Research Consortium
Funding Source and Program Name: Western Economic Diversification Canada
Amount and Duration: $1,500,000 over 3 years (2008 - 2010)

Title of Grant: Support for the Rederivation Facility
Funding Source and Program Name: Western Economic Diversification Canada
Amount and Duration: $260,300 over 5 years (2004 - 2008)

Title of Grant: University of British Columbia Centre for Disease Modeling
Funding Source and Program Name: Canada Foundation for Innovation (CFI)
Amount and Duration: $7,507,000 over 6 years (2004 - 2009)

(g) Conference Participation (Organizer, Keynote Speaker, etc.)

Conference Presentations

1. ***Jefferies, W.A.,*** Characterization of the rat transferrin receptor. Harden Conference on the Cell Surface Proteins of Lymphocytes, Kent, England, 1982.

2. ***Jefferies, W.A.***, A monoclonal antibody against rat transferrin receptor does not detectably label lymphopoietic stem cells. EMBO Workshop on T Lymphocyte Cloning, Marseille, France, 1983.

3. ***Jefferies, W.A.***, Structure of the CD4(W3/25) T-Helper Lymphocyte Glycoprotein, Biochemical Society, London, England, 1985.

4. ***Jefferies, W.A.***, Structure of the rat CD4(W3/25) glycoprotein of T helper lymphocytes. Sixth International Congress of Immunology, Toronto, Ontario, Canada, 1986.

5. ***Jefferies, W.A.***, Using antisense segments of the H-2 K^k to inhibit cell surface expression of MHC Class I proteins. H-2 and HLA Workshop, Montreaux, Switzerland, 1986.

6. ***Jefferies, W.A.***, The E3/19K protein of Adenovirus 2 binds to HLA molecules intracellular and inhibits recognition by cytolytic T lymphocytes, International Congress of Virology, Edmonton, Alberta, Canada, 1987.

7. ***Jefferies, W.A.***, A Null MHC Class I Restriction Element Becomes Functions in Transgenic Mice, H-2 and HLA Workshop, Airlie House, Virginia, U.S.A., 1988.

8. ***Jefferies, W.A.***, The Joint Swedish-Israeli Workshop on Biophysical Interactions, Stockholm, Sweden -Studies on MHC Class I molecules, 1988.

9. ***Jefferies, W.A.***, Using antisense RNA in the inhibition of H-2 molecules. EMBO/INSERM Workshop on Antisense RNA, Savoie, France, 1988.

10. ***Jefferies, W.A.***, Cytolytic T cells recognize a chimeric MHC Class I antigen expressed in influenza A infected transgenic mice. The Swedish-Israeli Workshop on the molecular basis of biological recognition, membrane dynamics and transport. Sodergarn Mansion, Stockholm, 1988.

11. ***Jefferies, W.A.***, A murine cell variant differentially presents antigens derived after VSV or Influenza infection. Taos, New Mexco, Keystone Symposium, 1992.

12. ***Jefferies, W.A.***, The adenovirus E3/19K protein blocks the phosphorylation of MHC molecules. Taos, New Mexico, Keystone Symposium, 1992.

13. ***Jefferies, W.A.***, Differentiated processing of viral and allogeneic peptides. Taos, New Mexco, Keystone Symposium, 1992.

14. ***Jefferies, W.A.***, Phosphorylation of MHC takes place in a Post-ER compartment, Canadian Society of Microbiologists, Vancouver, B.C., November, 1991

15. ***Jefferies, W.A.***, Canada Society for Immunology keynote speaker, Montreal, Quebec - The Adenovirus-2 E3/19K protein down regulates the host immune response. 1992.

16. ***Jefferies, W.A.***, Regulation of the Phosphorylation of MHC Class I molecules by the E3 region of Adenovirus Type 2, Canadian Society for Immunology, Lake Louise, Alberta, March 1993.

17. ***Jefferies, W.A.***, Molecular analysis of the F4/80 antigen, Canadian Society for Immunology, Lake Louise, Alberta, March 1993.

18. ***Jefferies, W.A.***, Expression of recombinant forms of Immunophillins in Baculovirus, Canadian Society for Immunology, Lake Louise, Alberta, March 1993.

19. ***Jefferies, W.A.***, TAP-1 is involved in peptide transport in the TAP-2-deficient RMA-S cell line. Canadian Society for Immunology, Lake Louise, Alberta, March 1995.

20. ***Jefferies, W.A.***, The Adenovirus protein E3/19K exhibits chaperone-like behaviour in the endoplasmic reticulum. Canadian Society for Immunology, Lake Louise, Alberta, March 1995.

21. ***Jefferies, W.A.***, A novel TAP transporter is peptide selective. Canadian Society for Immunology, Lake Louise, Alberta, March 1995.

22. ***Jefferies, W.A.***, Screening hybridomas by fluorescence concentration analysis. Canadian Society for Immunology, Lake Louise, Alberta, March 1995.

23. ***Jefferies, W.A.***, Restricted isoform expression and tyrosine phosphatase activity of CD45 in murine dendritic cells. Canadian Society for Immunology, Lake Louise, Alberta, March 1995.

24. ***Jefferies, W.A.***, Characterization of novel adenoviral protein and its ability to modulate MHC class I surface expression. Canadian Society for Immunology, Lake Louise, Alberta, March 1995.

25. ***Jefferies, W.A.***, Kennard, M.L., Gabathuler, R., Food, M. R., Yamada, T., McGeer, P. Studies on the melanotransferrin molecule. National Centre of Excellence, Neural regeneration Network, June, 1995, St. Adéle, Que.

26. ***Jefferies, W.A.***, Determination of the TAP transporters' specificity in the viral processing and presentation deficient cell line CMT.64. 23rd Meeting of the Federation of European Biochemical Societies, Basel, Suisse, August, 1995.

27. ***Jefferies, W.A.***, Characterisation of a GPI-linked protein, Melanotransferrin (p97), involved in transferrin-indepedent uptake of iron. 23rd Meeting of the Federation of European Biochemical Societies, Basel, Suisse, August, 1995.

28. ***Jefferies, W.A.***, Tap-1 is sufficient for the transport of selected peptides. 23rd Meeting of the Federation of European Biochemical Societies, Basel, Suisse, August, 1995.

29. ***Jefferies, W.A.***, Convenor ASM Meeting, Newport, Oregon, Persistence mechanisms of Viruses.

30. ***Jefferies, W.A.***, Serum levels of the Iron Binding Protein p97: A novel biological marker of Alzheimer's Disease. Fifth International conference Disease and related disorders, Osaka Japan, 24th July, 1996

31. ***Jefferies, W.A.***, Molecular Biology of Alzheimer's Disease, IBC Conference San Francisco, California, p97 and Alzheimer's Disease 1997

32. ***Jefferies, W.A.***, Serum p97 levels as a screening test for Alzheimer's disease. 6th International conference on Alzheimer's Disease and Related Disorders Amstersdam, The Netherlands 18-23 July, 1998

33. ***Jefferies, W.A,*** Human melanotransferrin binds to the human transferrin receptor in vitro. BioIron '99, World Congress on Iron Metabolism. Naples, Italy, May 1999

34. ***Jefferies, W.A,*** Metal binding properties of the novel iron binding protein, melanotransferrin (p97). BioIron '99, World Congress on Iron Metabolism. Naples, Italy, May 1999

35. ***Jefferies, W.A.,*** Transcytosis of p97 across the blood-brain barrier. American Society for Pharmacologists. New Orleans, Louisiana, November 1999

36. ***Jefferies, W.A.,*** Round Table discussion on Biomarkers of Alzheimer's Disease International Congress of Alzheimer's and related diseases, Amsterdam 1998

37. ***Jefferies, W.A.,*** Toward a Comprehensive Theory for Alzheimer's Disease Orlando Florida, AD Association 1998

38. ***Jefferies, W.A.,*** Gordon Conference, Barriers of the Central Nervous System. New Hampshire, USA. 2002

39. ***Jefferies, W.A.,*** Annual Canadian Vaccine Meeting. Toronto, Ont., Canada. 2002

40. ***Jefferies, W.A.,*** Progress in Vaccination against Cancer (PIVAC). British Society for Immunology. Nottingham, England. 2002

41. ***Jefferies, W.A.,*** Keystone Conference – Tumor Immunology Keystone, Colorado 2003

42. ***Jefferies, W.A.,*** Keystone Conference – Tumor Immunology II. Keystone, CO 2005

43. ***Jefferies, W.A.,*** 9th International Symposium on Dendritic Cell - Edinburgh, Scotland (delivered by graduate student Robyn Seipp) September 2006

44. ***Jefferies, W.A.,*** Vaccines on the Horizon - 7th Canadian Immunization Conference, Winnipeg, MB 2006

45. ***Jefferies, W.A.,*** Prostate Cancer Research Retreat, Canadian Prostate Cancer Research Foundation, Oakley, ON (delivered by graduate student Francesca Setiadi). February 2007

46. ***Jefferies, W.A.,*** Vaccine Evaluation Centre, Vancouver, BC April 2007

47. ***Jefferies, W.A.,*** Keystone Conference – Cancer Vaccines. Banff, AB March/April 2007

48. ***Jefferies, W.A.,*** Cerebral Vascular Biology Conference, Ottawa, ON June 2007

49. ***Jefferies, W.A.,*** Gordon Conference, Antigen Cross-Presentation, Big Sky Montana, Sept 2-7, 2007

50. ***Jefferies, W.A.***, T.Z. Vitalis, Q.J. Zhang, J. Alimonte, G. Basha, A.R. Moise, Vaccine Congress, Amsterdam, The Netherlands, December 9-11, 2007

51. ***Jefferies, W.A.*** Canadian Society for Immunology and Cancer Immune Therapy Symposium, Whistler, BC Canada, April 3-6, 2009, Tumor Immune Therapy: Trials and Tribulations

10. SERVICE TO THE UNIVERSITY

(a) Memberships on committees, including offices held and dates

1. 1990-2001: Founder and Organizer of the Campus Wide Immunology Study Group
2. 1990-present: Member U.B.C. Biochemical Discussion Group
3. 1990-present: Member U.B.C. Immunology Seminar Group
4. 1991: Chairman, Department of Microbiology, Pathogenesis Course Evaluation Committee
5. 1991: Member, Department of Microbiology, Immunology Course Evaluation Committee
6. 1991: Member, Department of Microbiology, Cell Biology Course Evaluation Committee
7. 1991: Member, Department of Microbiology, Immunology Curriculum Committee
8. 1992: Medicine 2000 Immunology/Transplantation Organizing Committee
9. 1992: Secretary Biotechnology Safety Committee
10. 1993: Member, Adhoc Committee, Microbiology 200
11. 1993: Secretary Biotechnology Safety Committee
12. 1993: Member, Undergraduate Genetic courses Evaluation Committee, Medical Genetics
13. 1995-2001: Graduate Council Representative for the Department of Microbiology and Immunology
14. 1996: Chairman Biotechnology Laboratory Awards Committee
15. 1997: Faculty of Science committee for Dissertation Gold Medal
16. 1998: Search Committee, Biotechnology Laboratory, Instructor position
17. 1998: Tenure Committee, Microbiology and Immunology, Michael Gold
18. 1998: Search Committee, Microbiology and Immunology, Virology Position
19. 1998: Committee to review B.C. Biotechnology Alliance High School Research Applications
20. 1998-2000: Director, U.B.C. Centre for Molecular Immunology
21. 2000-present: Principal Investigator, CANVAC
22. 1998-2000: Organizing Campus Wide Transgenic Animal Facility
23. 2000-present: Director of UBC Transgenic and Knockout Facility
24. 2000-present: Member of the UBC Animal Users Committee

25. 2004-present: Director of UBC Rederivation Facility
26. 2005-present: Member of TRID (CHIR-UBC Strategic Training Program for Translational Research in Infectious Diseases) Faculty Member
27. 2006-present: Co-Director of the TransArc Network
28. 2006-present: Participant in the Centre for Drug Research and Development
29. 2006-present: Centre for Blood Research at UBC, Faculty Member
30. 2007-present: Co-Director of the BC Pre-Clinical Research Consortium (BC-PRC)
31. 2008: Tenure Committee, Zoology, Nelly Pante
32. 2008: Tenure Committee, Microbiology and Immunology, Marc Horwitz

(b) Other service, including dates

1. 1989: U.B.C. Program for Effective Teaching Methods -One day seminar
2. 1991: U.B.C. Program for Effective Teaching Techniques-Three day seminar
3. 2002: UBC Transgenic Animal Techniques Course offered to research community

11. SERVICE TO THE COMMUNITY

(a) Memberships on scholarly societies, including offices held and dates

1. 1982- present British Biochemical Society
2. 1982-1989 British Transplantation Society
3. 1982- present British Society of Immunology
4. 1990-present Canadian Society of Immunology
5. 1998-2000 Director of the Centre for Molecular Immunology
6. 2001-2003 BC Biotechnology Awards Committee, Chairman
7. 2005-2007 NRC Advisory Board, Ottawa, Canada

(b) Memberships on other societies, including offices held and dates

(c) Memberships on scholarly committees, including offices held and dates

1. Member of the Ronald and Nancy Alzheimer's Research Association committee on Emerging Biomarkers for Alzheimer's Disease

2. "The Consensus Report of the Working Group on: 'Molecular and Biochemical Markers of Alzheimer's Disease,' which appears in the April 1998 issue of the journal Neurobiology of Aging.

3. 1991-92 National Cancer Institute of Canada fellowship, scholarship, and career award panel member

4. 1992-93 National Cancer Institute of Canada, Immunology Grants Committee

5. 1993-94 National Cancer Institute of Canada, Immunology Grants Committee

6. 1998-2001 Canadian Institutes for Health Research Immunology panel

7. 2000-2004 Alberta Heritage Fund and Career Award committee

(d) Memberships on other committees, including offices held and dates

e) Editorships (list journal and dates)

1. 2000-2001 International Journal of Cancer, Editor

2. Jan 2001-Dec 2002: Journal of Alzheimer's Disease, Associate Editor

(f) Reviewer (journal, agency, etc. including dates)

Peer Reviews: Grants

1. 1990 - Natural Science and Engineering Research Council of Canada Operating grant
2. 1990 - Natural Science and Engineering Research Council of Canada Strategic grant
3. 1991 - Natural Science and Engineering Research Council of Canada Strategic grant
4. 1991 - Medical Research Council of Canada Operating grants
5. 1991/92 - Medical Research Council of Canada grants
6. 1991 - St. Paul's Hospital Foundation Grant
7. 1992- National Cancer Institute of Canada, Career Fellowships
8. 1992- Alberta Cancer Society grant
9. 1992-93 - Medical Research Council of Canada Operating grants
10. 1992-93 - National Cancer Institute of Canada Operating grants
11. 1993-94 - Medical Research Council of Canada Operating grants
12. 1993-94 - National Cancer Institute of Canada Operating grants
13. 1994- Alberta Cancer Society grant
14. 1996 Medical Research Council of Canada Operating grants

15. 1997 Medical Research Council of Canada Operating grants
16. 1997- Manitoba Research Foundation
17. 1998 Medical Research Council of Canada Operating grants
18. 1998- Manitoba Research Foundation
19. 1998- Dalhousie Research Foundation
20. 1998- Heart and Stoke Foundation
21. 2000-02 Canadian Network for Vaccines and Immunotherapeutics of Cancer and Chronic Viral Disease
22. 2001-02 BCRP Concept Award: U.S. Army Medical Research Acquisition Activity
23. 2001-04 National Cancer Institute
24. 2001-02 CANFAR

Peer Reviews: Journals

1. FEBS Letters
2. International Immunology
3. Biochem Biophys Acta
4. Journal of Neuroscience
5. Blood
6. Journal of Leukocyte Biology
7. Pharmacology, Biochemistry and Behavior
8. European Journal of Immunology
9. Nature Medicine
10. FASEB
11. Journal of Immunology
12. Nature Immunology
13. Cancer Research
14. Journal of Alzheimer Disease
15. International Journal of Cancer

National Grant Review Panels

1. 1992 National Cancer Institute of Canada Career Award and Fellowship Panel
2. 1993 National Cancer Institute of Canada Immunology Panel

3. 1994 National Cancer Institute of Canada Immunology Panel
4. 1999-2000 Canadian Institutes of Health Research, Immunology and Transplantation Panel
5. 2006 Canadian Institutes of Health Research, Immunology and Transplantation Panel

(g) External examiner (indicate universities and dates)

1. Mark Luscher Ph. D., University of Toronto, Brian Barber (supervisor) 2004

(h) Consultant (indicate organization and dates)

1. 1997-2003: Board of Directors, Synapse Technologies Incorporated.
2. 2000-2005: Board of Directors, GeneMax Pharmaceuticals Incorporated
3. 2005-present: Scientific consultant, TapImmune Incorporated
4. 2008: Scientific consultant , biOasis Technologies Incorporated

(i) Other service to the community

1. 1990: Host of the EUCLID recipients, Award winners of the province wide Math prizes
2. 1990: Host Organizer/Lecturer of U.B.C. Connect 90' B.C. High School Science Student Forum
3. 1990: Faculty Representative at the Convocation Ceremonies for the Faculty of Science
4. 1990: Faculty of Science, Open House Display
5. 1991: Lecturer: Three day seminar U.B.C. Connect 91' B.C. High School Science Student Forum
6. 1991: Judge for the Canada Wide Science Fair for Canadian High School Students
7. 1991: Faculty Representative at the U.B.C. Convocation Ceremonies for the Faculty of Science
8. 1991: OUTREACH Volunteer for U.B.C participation in High School Graduation Ceremonies
9. 1992: Faculty Representative at the U.B.C. Convocation Ceremonies for the Faculty of Science
10. 1992: University sponsored lecture: Shad Valley Program
11. 1993: Faculty Representative at the U.B.C. Convocation Ceremonies for the Faculty of Science
12. 1993: University sponsored lecture: Shad Valley Program for exceptional B.C. High school students

13. 1993-Present: Lecturer: Three day seminar U.B.C. ***Connect*** B.C. High School Science Student Forum

14. 1998: Supervised High School Co-op Research Projects

15. 1994 - present: Soccer Coach for White Rock league.

12. AWARDS AND DISTINCTIONS

(a) Awards for Teaching (indicate name of award, awarding organizations, date)

(b) Awards for Scholarship (indicate name of award, awarding organizations, date)

1. 1985 Lady Tata Memorial Leukemia Fellowship
2. 1985 Royal Society of London Postdoctoral Fellowship
3. 1985-86 Welcome Trust Postdoctoral Fellowship
4. 1986-89 Medical Research Council of Canada Postdoctoral Fellowship
5. 1990 University Nominated for Hughes Institutes for Medical Research Centre
6. 1994 Named Principal Investigator for the National Network of Excellence for Neural Regeneration
7. 1995 University Nominated for Hughes Institute for Medical Research International Scholarship
8. 2001-2002 University Killam Faculty Research Fellowship
9. 2008: Wiederhelm Award, The Federation of American Societies for Experimental Biology

(c) Awards for Service (indicate name of award, awarding organizations, date)

(d) Other Awards

Academic awards and distinctions (prior to final degree)

1. 1980 British Columbia Cancer Research Summer Scholarship
2. 1982-1985 Overseas Research Student Scholarship (British)
3. 1982-84 British Columbia Health Care Trainingship Award
4. 1982 Natural Science and Engineering Council of Canada Graduate Scholarship
5. 1982-85 Royal Commission for Exhibition of 1851 Scholarship (London)

13. OTHER RELEVANT INFORMATION

Publications Record

Date: April 23, 2009

SURNAME: JEFFERIES **FIRST NAME:** Wilfred **MIDDLE NAME(S):** Arthur

	Summary of Refereed Publications		Summary of Non-Refereed Publications		
	1A *(journals)*	1B *(reviews)*	2 *(conf. pro.)*	3 *(books)*	4 *(patents)*
Career	**70**	**8**	**100**	**5**	**40**
Last 5 Years	**19**	**2**	**25**	**2**	**4**

1. REFEREED PUBLICATIONS

(a) Journals (* denotes publications of primary importance)

1. ***Jefferies WA**, Brandon MR, Hunt SV, Williams AF, Gatter KC, Mason DY. (1984) Transferrin receptor on endothelium of brain capillaries. **Nature** 312: 162-163.

2. **Jefferies WA**, Brandon MR, Williams AF, Hunt SV. (1985) Analysis of lymphopoietic stem cells with a monoclonal antibody to the rat transferrin receptor. **Immunology** 54: 333-341.

3. **Jefferies WA**, Green JR, Williams AF. (1985) Authentic T helper CD4 (W3/25) antigen on rat peritoneal macrophages. **J. Exp. Med.** 162: 117-127.

4. Arvieux J, **Jefferies WA**, Paterson DJ, Williams AF, Green JR. (1986) Monoclonal antibodies against a rat leukocyte antigen block antigen-induced T-cell responses via an effect on accessory cells. **Immunology** 58: 337-342.

5. ***Jefferies WA**, Barclay AN, Gagnon J, Williams AF. (1986) Structure of the CD4(W3/25) T-helper lymphocyte glycoprotein. **Biochemical Society Transactions** 14(2): 336.

6. Paterson DJ, Green JR, **Jefferies WA**, Puklavec M, Williams AF. (1986) The MRC OX-44 antigen marks a functionally relevant subset among rat thymocytes. **J. Exp. Med.** 165: 1-13.

7. *Clark SJ, **Jefferies WA**, Barclay AN, Gagnon J, Williams AF. (1987) Peptide and nucleotide sequences of rat CD4(W3/25) antigen: evidence for derivation from a structure with four immunoglobulin-related domains. **Proc. Natl. Acad. Sci. U.S.A.** 84: 1649-1653.

8. Crocker PR, **Jefferies WA**, Clark SJ, Chung PL, Gordon S. (1987) Species heterogeneity in macrophage expression of the CD4 antigen (AIDS virus receptor). **J. Exp. Med.** 166: 613-618.

9. **Jefferies WA** and MacPherson GG. (1987) Expression of the W6/32 HLA class I epitope by cells of rat, mouse, human and other species: critical dependence on the interaction of specific MHC heavy chains with human and bovine beta 2-microglobulin. **Eur. J. of Immunol,** 17: 1257-1263.

10. Paterson DJ, **Jefferies WA**, Green JR, Brandon MR, Corthesy P, Puklavec MJ, Williams AF. (1987) Antigens of activated rat T lymphocytes including a molecule of 50,000 Mr detected only on CD4 positive T cell blasts. **Molecular Immunology** 24: 1281-1290.

11. ***Jefferies WA**, Ruther U, Wagner EF, Kvist S. (1988) Cytolytic T cells recognize a chimeric MHC class I antigen expressed in influenza A infected transfenic mice. **EMBO Journal** 7: 3423-3431.

12. **Jefferies WA** and Burgert H-G. (1990) E3/19k from Adenovirus 2 is an immunosubversive protein that binds to a structural motif regulating the intracellular transport of major histocompatibility complex class I proteins. **J.Exp. Med.** 172: 1653-1664.

13. Lippé R, Luke E, Kauh Y-T, Lomas C, **Jefferies WA.** (1991) Adenovirus infection inhibits the phosphorylation of major histocompatibility complex class I proteins. **J. Exp. Med.** 174: 1159-1166.

14. Matsuse T, Hayashi S, Kuwano K, Keunecke H, **Jefferies WA**, Hogg JC. (1992) Latent adenoviral infection in the pathogenesis of chronic airways obstruction. **Am. Rev. Respir Dis.** 146: 177-184.

15. Michaelis C, Banfield B, Gruenheid S, Tsang Y, Lippé R, **Jefferies WA**, Wattenberg B, Tufaro F. (1992) Toxin resistance and reduced secretion in a mouse L-cell mutant defective in Herpes Virus propagation. Biochemistry and Cell Biology, anniversary edition. **Biochem and Cell Biol.** 70: 1209-1217

16. Ou D, Chong P, Choi Y, McVeigh P, **Jefferies WA**, Gerasimos K, Tingle A.J, Gillam S. (1992) Identification of T-cell epitopes on E2 protein of rubella virus, as recognized by human T-cell lines and clones. **J. Virology** 66: 6788-6793.

17. Ou D, Chong P, McVeigh P, **Jefferies WA**, Gillam S. (1992) Characterization of the specificity and genetic restriction of human CD4+ cytotoxic T cell clones reactive to capsid antigen of rubella virus. **Virology** 191: 680-686.

18. Kennard M, Food M, **Jefferies WA**, Piret J. (1993) Controlled release process to recover heterologous glycosylphosphatidylinositol anchored proteins from CHO cells. **Biotechnology and Bioengineering** 42: 480-486.

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60. Kotturi, M.F. and **Jefferies, W.A.** Expression of a Novel Voltage-Dependent Calcium Channel in Human T Lymphocytes. Keystone Symposia on Lymphocyte Activation and Signaling, Steamboat Springs, Colorado. Jan. 8-13, 2004.

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62. Scipp, R.P., Moise, A.R., Lok, S., and **Jefferies, W.A.** Characterization of a TAP (Transporter Associated with Antigen Processing) Fusion Protein. 12th International Congress of Immunology and 4th Annual Conference of FOCIS, Montreal, Quebec. July 18-23, 2004

63. Setiadi AF, Chen SS, and **Jefferies WA.** Identification of the Underlying Mechanisms of Transporter Associated with Antigen Processing (TAP) Deficiency in Carcinomas. Clinical and Investigative Medicine Journal Supplement 2004; 27(4): 176D. 12th International Congress of Immunology and 4th Annual Conference of FOCIS, Montreal, QC, Jul. 18-23, 2004.
64. Dickstein, D.L., Jeffries, A.R. and **Jefferies, W.A.** Aß immunization restores blood-brain barrier integrity in the Tg2576 AD model mouse. The 9th International Conference on Alzheimer's disease and Related disorders. Philadelphia, PA. July 18-22, 2004.
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67. RP Seipp, A Moise, S Lok, **W Jefferies.** Characterization of a TAP (Transporter associated with antigen processing) fusion protein. Keystone Symposia.Dendritic Cells (B2) February 1-7 2005. Vancouver BC, Canada.
68. R. Seipp, SS Chen, QJ Zhang, TZ Vitalis, XL Li, KB Choi, A Jeffries, **WA Jefferies**, TAP expression reduces IL-10 expressing tumour infiltrating lymphocytes and restores immunosurveillance against melanoma. 9th International Conference on Dendritic Cells, Edinburgh, Scotland September 16-20, 2006.
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73. Kyla Omilusik, Matt Finlay, Gregory Lizée, and **Wilfred A. Jefferies**. MHC I Down-regulation in Nef-expressing Dendritic Cells. Keystone Conference: HIV Vaccines and HIV Pathogenesis. Whistler, BC. March 25-30 2007
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77. Mei Mei Tian, Jacqueline Tiong, Garnet Martens, Timothy Vitalis and **Wilfred Jefferies**. A novel iron uptake pathway by GPI-anchored p97 in mammalian endothelial cells. 7th Cerebral Vascular Biology International Conference. June 24-28, 2007

78. K. Biron, D.L. Dickstein, K.B. Choi, B. Chung, J. Lee and **W.A. Jefferies**. Amyloid-beta regulates expression of melanotransferrin in microglia. 7th Cerebral Vascular Biology International Conference. June 24-28, 2007

79. Kyla Omilusik, Genc Basha, Gregory Lizée, Anna Reinicke, Robyn P. Seipp, and **Wilfred A. Jefferies** MHC Class I Trafficking and exogenous antigen loading in dendritic cells is differentially regulated by distinct cytoplasmic tail motifs. Gordon Conference Antigen Cross-Presentation, Big Sky MT, Sept. 2-7, 2007.

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(d) BOOKS

(e) Chapters

1. **Jefferies WA.** (1988). Hemopoietic and T Lymphocyte Marker Antigens of the Rat characterized with monoclonal antibodies, Chapter 6, p. 178-248 in Differentiation Antigens in Lymphohemopoietic Tissues. Eds. Miyasaka M, Trnka Z, Marcel Dekker, New York and Basel.

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5. Walker B.L., Tiong J.W.C., **Jefferies W.A.** (2001) Iron Metabolism in Mammalian Cells. **International Review of Cytology,** 211:241-78.

14 PATENTS

File Date	Country	Status	Patent Title	Patent No.	Issue Date
09/22/1995	Japan	Notice of Allowance	Method of Enhancing Expression of MHC-Class 1 Molecules Bearing Endogenous Peptides		
08/17/2001	PCT	National waived	Chemotherapeutic Agents Conjugated to p97 and Their Methods of Use in Treating Neurological Tumours		
02/08/2001	PCT	National Phase	Compositions and Methods for Screening Therapeutic Agents		
02/23/2001	PCT	National Phase	Novel Circular Extra-Chromosomal DNA Elements		
12/07/2001	PCT	National Phase	CAML Modulation Proteins		
06/07/2000	PCT	National Phase	Apoptosis Inhibition by Adenovirus E3/6.7K		
09/22/1995	PCT	National Phase	Method of Enhancing Expression of MHC-Class 1 Molecules Bearing Endogenous Peptides		
03/12/1997	PCT	National Phase	Method of Identifying MHC-Class I Restricted Antigens Endogenously Processed By a Cellular Secretory Pathway	WO 97/34143	09/18/1997
08/30/1996	PCT	National Phase	Use of p97 and Iron Binding Proteins as Diagnostic and Therapeutic Agents		
07/09/1993	PCT	National Phase	Use of p97 and Iron Binding Proteins as Diagnostic and Therapeutic Agents		
07/31/2002	Australia	Issued	Compositiona and Methods for Screening Therapeutic Agents	785028	12/14/2006
09/22/1995	European	Issued	Method of Enhancing Expression of MHC-Class 1 Molecules Bearing Endogenous Peptides	0783573	12/21/2005
03/21/1997	USA	Issued	Method of Enhancing Expression of MHC-Class 1 Molecules Bearing Endogenous Peptides	6,361,770	03/26/2002
03/12/1997	Switzerland	Issued	Method of Identifying MHC-Class I Restricted Antigens Endogenously Processed by a Cellular Secretory Pathway	0888540	07/23/2003
03/12/1997	Finland	Issued	Method of Identifying MHC-Class I Restricted Antigens Endogenously Processed by a Cellular Secretory Pathway	0888540	07/23/2003
03/12/1997	Canada	Issued	Method of Identifying MHC-Class I Restricted Antigens Endogenously Processed by a Cellular Secretory Pathway	2,248,651	09/07/2004
03/12/1997	Japan	Issued	Method of Identifying MHC-Class I Restricted Antigens Endogenously Processed By a Cellular Secretory Pathway	3,805,792	05/19/2006
03/12/1997	European	Issued	Method of Identifiying MHC-Class I Restricted Antigens Endogenously Processed By a Cellular Secretory Pathway	0888540	07/23/2003
03/12/1996	USA	Issued	Method of Identifying MHC-Class I Restricted Antigens Endogenously Processed By a Cellular Secretory Pathway	5,792,604	08/11/1998

03/12/1997	Italy	Issued	Method of Identifying MHC-Class I Restricted Antigens Endogenously Processed by a Cellular Secretory Pathway	0888540	07/23/2003
03/12/1997	Germany	Issued	Method of Identifying MHC-Class I Restricted Antigens Endogenously Processed By a Cellular Secretory Pathway	0888540	07/23/2003
03/12/1997	Sweden	Issued	Method of Identifying MHC-Class I Restricted Antigens Endogenously Processed by a Cellular Secretory Pathway	0888540	07/23/2003
03/12/1997	UK	Issued	Method of Identifying MHC-Class I Restricted Antigens Endogenously Processed by a Cellular Secretory Pathway	0888540	
03/21/1997	France	Issued	Method of Identifying MHC-Class I Restricted Antigens Endogenously Processed by a Cellular Secretory Pathway	0888540	07/23/2003
08/30/1996	Australia	Issued	Quantitation of p97 to Diagnose and Monitor Alzheimer's Disease	717198	07/06/2000
08/30/1996	New Zealand	Issued	Quantitation of p97 to Diagnose and Monitor Alzheimer's Disease	315997	12/20/1999
04/01/1999	USA	Issued	Use of p97 and Iron Binding Proteins as Diagnostic and Therapeutic Agent	6,455,494	09/24/2002
08/30/1996	Israel	Issued	Use of p97 and Iron Binding Proteins as Diagnostic and Therapeutic Agents	123441	04/15/2001
08/31/1995	USA	Issued	Use of p97 and Iron Binding Proteins as Diagnostic and Therapeutic Agents	5,981,194	11/09/1999
07/09/1993	European	Issued	Use of p97 in the Diagnosis of Alzheimer Disease	EP 0651768	11/07/2001
08/30/1996	European	Issued	Use of p97 and Iron Binding Proteins as Diagnostic and Therapeutic Agents	0847530	06/16/2004
02/08/2001	Canada	Filed	Compositions and Methods for Screening Therapeutic Agents		
02/08/2001	European	Filed	Compositions and Methods for Screening Therapeutic Agents		
08/08/2002	Japan	Filed	Compositions and Methods for Screening Therapeutic Agents		
11/30/2006	PCT	Filed	Pox Viridae Treatment		
12/18/2006	Canada	Filed	Anti-Tumour Immunity and Specific T Cell Memory are Induced by Low Dose Inoculation with Nonreplicating Recombinant Adenovirus Encoding TAP1		
01/16/2002	USA	Filed	Method of Enhancing An Immune Response		
07/09/1993	European	Filed	Use of p97 and Iron Binding Proteins as Diagnostic and Therapeutic Agents		
07/09/1993	Canada	Filed	Use of p97 and Iron Binding Proteins as Diagnostic and Therapeutic Agents		
08/30/1996	Canada	Filed	Quantitation of p97 to Diagnose and Monitor Alzheimer's Disease		

Technology Disclosure

1991 Peptides for use in modulation the expression of Human receptors: a general approach.
Co-discoverer: ***W. A. Jefferies***, Mr. G. Kolaitis

Licensed Processed:

1. Beta-emission enhancement solution
Co-discoverer: Drs. ***W. A. Jefferies***, R. Gabathuler
Licensed to Dragon Consultant, May, 1993.

15. SPECIAL COPYRIGHTS

16. ARTISTIC WORKS, PERFORMANCES, DESIGNS

17. OTHER WORKS

18. WORK SUBMITTED (including publisher and date of submission)

Refereed papers, submitted

1. Genc Basha, Kyla Omilusik, Anna Reinicke, Kyung Bok Choi, and **Jefferies WA**. An alternative function for the invariant chain in MHC Class I cross presentation and cross-priming in dendritic cells is differentially regulated by distinct cytoplasmic tail motifs. **Submitted to Nature Immunology.**

2. Kotturi M, Cherneski C, Levin A, and **Jefferies WA**. Immunosuppressive impact of common calcium blockers in renal disease patients. **Submitted to Hypertension.**

3. Yiwen Teresa Wang, Xiaoxi Chen, Kyla Omilusik, John J. Priatel, Kyung Bok Choi, Rayshad Gopaul, Hung-Sia Teh, N. Torben Bech-Hansen, **Wilfred A. Jefferies** Life, Death and Exhaustion: Tonic Signals Mediated by L-type Ca^{2+} Channels Promote Naïve CD4 and CD8 T Cell Survival. **In revision to Nature Immunology.**

4. Laura Johnson, Fang Zhang , Genc Basha , Robyn Seipp , Anna Chan , Renxue Wang , Victor Ling , **Wilfred Jefferies**. TAPL Orchestrates Dendritic Cell Antigen Sampling and Regulates Lymphocyte Cellularity. **Submitted to PlosOne.**

5. Reinicke A, Omilusik K, Basha G, Jefferies WA. Dendritic Cell Crosspriming is Indispensable for Immunity to Bacteria. **Submitted to PLoS Pathogens.**

6. Dara L. Dickstein, KB Choi, Brian Chung, Janet Lee, and Wilfred A. Jefferies. Amyloid beta Regulated Expression of Melanotransferrin in Microglia is inhibited by NSAIDS. **In revision.**

7. Jacqueline W.C. Tiong Mei Mei Tian, Garnet Martens, Elaine C. Humphrey, Tim Z.Vitalis and **Wilfred A. Jefferies.** Iron uptake in mammals mediated through the internalization of GPI-anchored p97 into caveolae. **In revision.**

19. SUMMARY OF RESEARCH:

Impact of Research: In the past year, my group published 6 journal articles in a number of high-impact journals, 2 are accepted for publication and we have submitted 4 more for publication. We had a so-called "breakthrough" paper in the last year, scientifically summarized and highlighted by the following web link (http://epigenome.eu/en/2,54,1052). We published this study in the ***Journal of Moleular and Cellular Biology***. In it we demonstrated that epigenetic mechanisms involving histone acetylation creates an "invisibility cloak" for certain cancer cells and allows them to hide from the immune system. This was covered by the worldwide press and appeared in Science Daily (http://www.sciencedaily.com/releases/2007/11/071108130155.htm) amongst other international science news sources. The impact of this study is that it will likely lead to new therapies that will force the cancer cells to "drop the cloak of invisibility" and be recognized by the immune system.

We published three papers using TAP-1 constructs to demonstrate that re-expression of TAP-1 reduces tumorgenicity and metastasis in syngeneic mice in vivo. One study in published in Vaccine, demonstrated long term memory responses against solid tumours after inoculation with viral constructs expressing TAP_1. One study published in International Journal of Cancer highlighted that inoculation with TAP-1 reduces the immuno-inhibitory cytokine profiles in solid tumours,. Another study that was published in ***Clinical Cancer Research*** demonstrated tha combining another antigen protein machinery component called Tapsasin with TAP-1 further enhances the immune respnse against tumours and reduces the tumour burden resulting in a high tumour free incidence. as a while the other highlighted the reduction in tumorgenicity in melanomas expressing TAP-1. These finding are significant because they show that the antigen processing defect in these carcinomas reduces tumour recognition in vivo and they highlight the potential of TAP(s) to augment immune responses in an MHC unrestricted manner, thereby alleviating the need to identify the exact tumour antigen from each individual tumour. The point the way toward a method for immune therapy against many types of metastatic tumours. It also supports the evidence that loss of expression to TAP is a prognosticator of outcome in cancer. Our lab was a pioneer in this area that has now spawned over 200 other scientific publications relating to our initial findings.

We publish a paper describing a unique viral immunosubversion mechanism, involving a small adenoviral protein which mimics a host cell protein, thereby tricking the cell into postponing apoptosis. This is an extremely important finding since viral infection of cells normally triggers cell death pathways. The ability of adenoviruses to subvert this apoptosis pathway has been known for many years, yet the E3-6.7K protein described in our paper has never been linked to this pathway, and indeed has long been thought to be too small to have significant effect.

In addition, we published an important review paper in ***Trends in Pharmacological Science*** regarding calcium channels that control T cell activation, which highlights calcium channels as the master switch in controlling T cell responses. This follows a paper we published the year before describing the molecular identity of channels that control T cell activation. Other researchers have long pursued this but our paper in ***Molecular Immunology*** was the first to clone and identify the molecular features of the channel that appears to be the master switch in controlling T cell responses. As such it is also a key target for identifying new classes of immune therapeutics. We were invited by he Editor of ***Nature Immunology*** to submit our work describing the immune-abnormalities of mouse lacking a lymphocyte calcium channel. It has been sent out for a formal review.

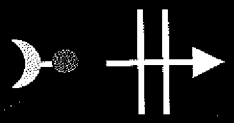
We will soon publish a paper in the high impact journal PloS One, entitled, **A Unique Carrier for Delivery of Therapeutic Compounds for Treatment of Neurological Diseases that Lay Beyond the Blood-Brain Barrier**. As therapeutic intervention in many neurological diseases is thwarted by the physical obstacle formed by the blood-brain barrier (BBB) that excludes most drugs from entering the brain from the blood, identifying efficacious modes of drug delivery to the brain remains a "holy grail' in molecular medicine and nanobiotechnology. This study provides the initial proof of concept for any protein-based carrier capable of shuttling therapeutic levels of drugs from the blood to the brain for the treatment of neurological disorders, including classes of resident and metastatic brain tumors. It may be prudent, therefore, to consider implementation of this novel delivery platform in various clinical settings for therapeutic intervention in acute and chronic neurological diseases.

Finally, I received the **Wiederhelm Award from FASEB and the Microcirculatory Society for publishing the highest impact and most highly cited study in this area of science for the years 2003-2007.** This study, by Ujiie M., Dickstein D., Carlow D., and **Jefferies, W.A.** (2003) Blood-brain barrier permeability precedes senile plaque formation in an Alzheimer disease model. **Microcirculation** 10, 463-470, is considered a seminal finding in the field as it reveals aspects of AD pathogenesis previously unexplained and it describes new methods for intervening in the disease. It was the subject of a keynote address I made at the ***International Cerebral Vascular Biology Conference*** last year and seems to have spawned growth in understanding the role of the BBB in many diseases.

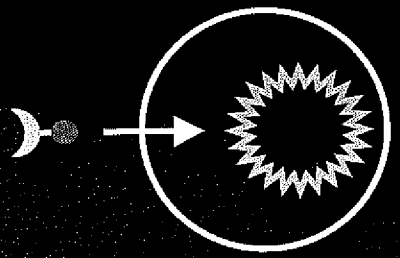
Exhibit B

Desirable Properties of Protein Carriers for Lysosomal Enzyme Delivery to the Brain

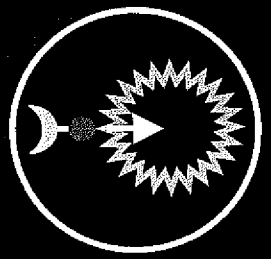
Transcytosed across BBB



Endocytosed by parenchymal cells



Transported to the lysosome



No effect upon enzyme function



Exhibit C

An *in vitro* model of the blood-brain barrier

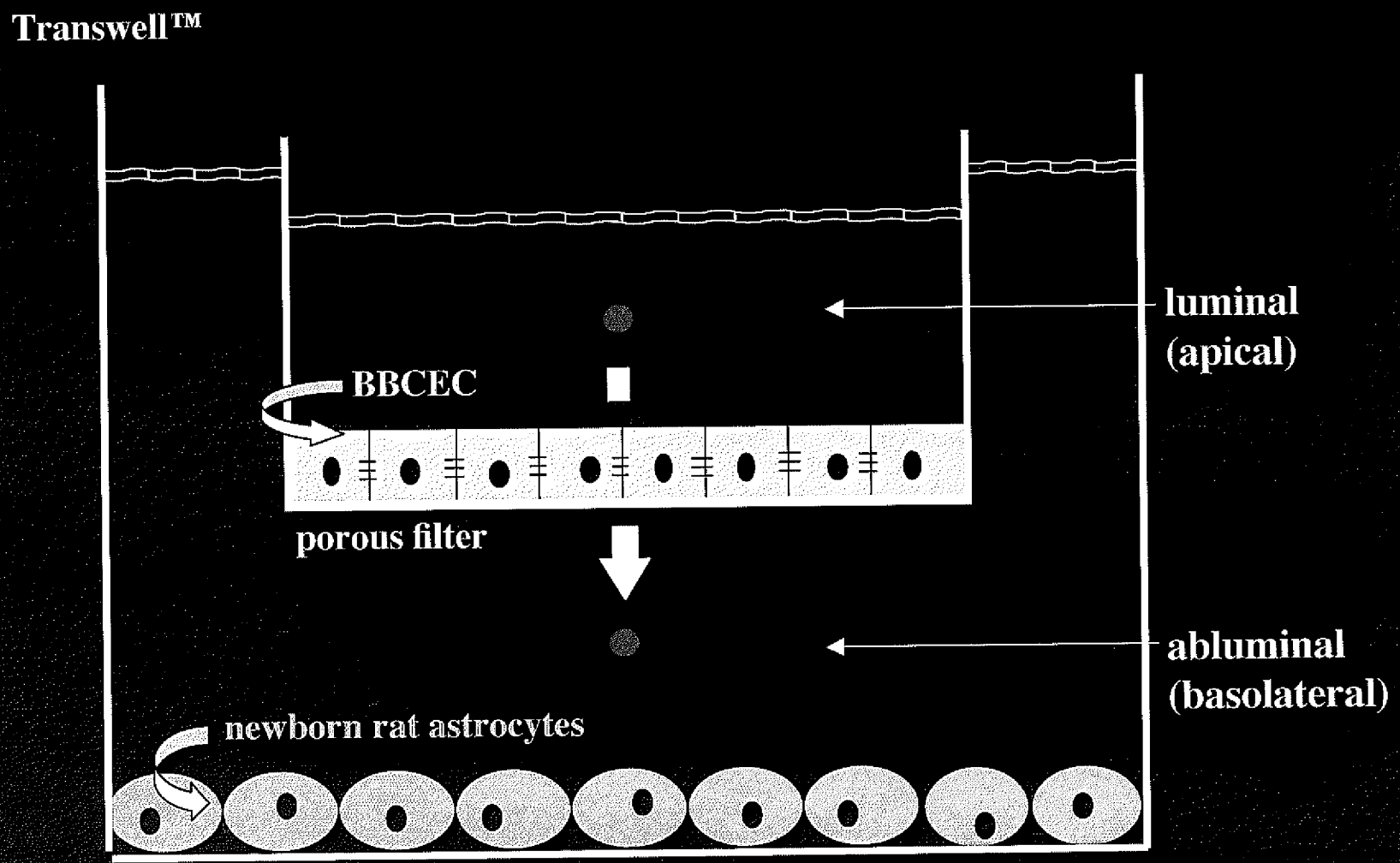
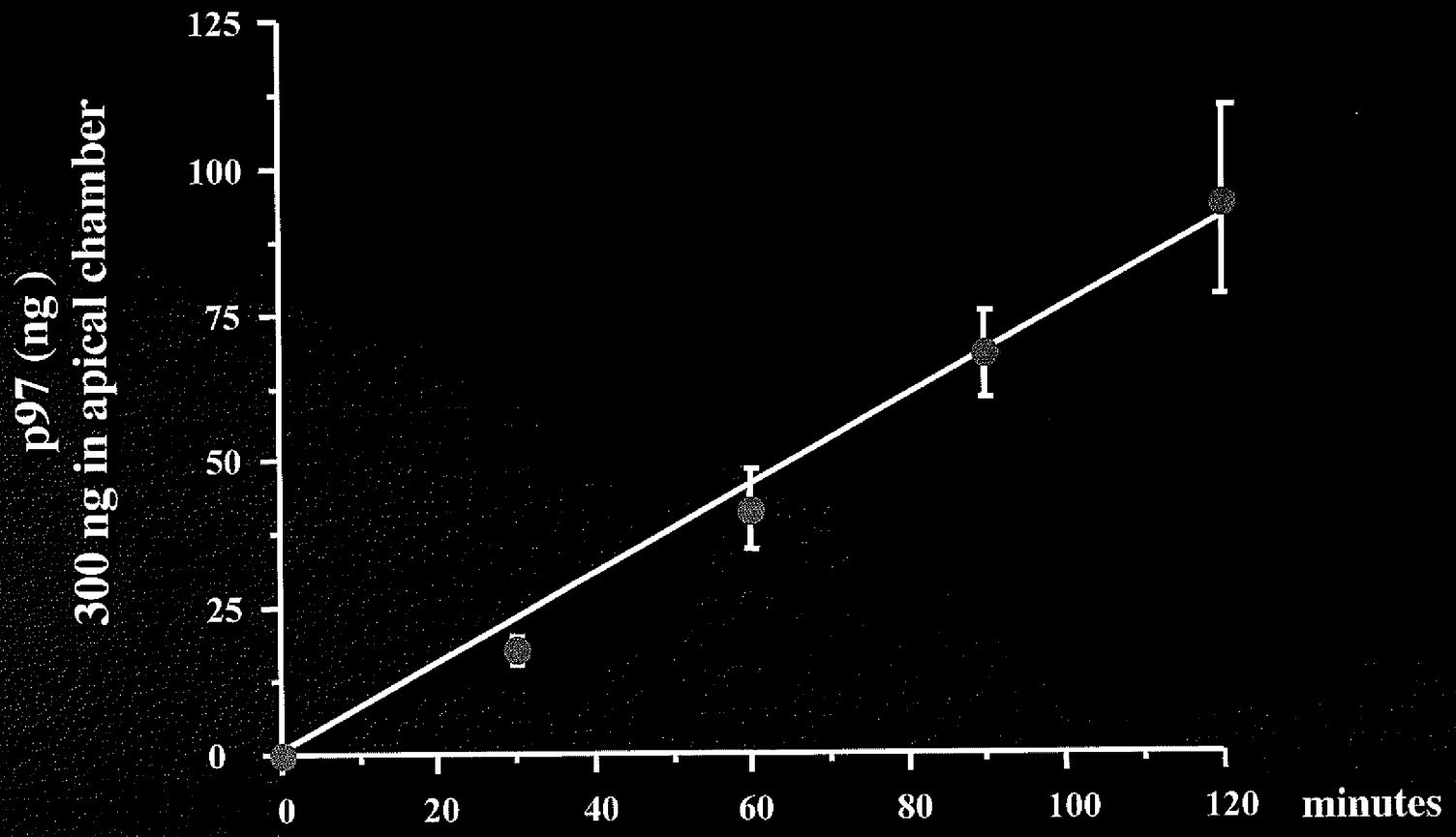


Exhibit D

Transcytosis of p97 in the *in vitro* BBB model



Beliveau et al.
Journal of Neurochemistry, accepted for publication

Transport is negligible at 4°C
Transport is saturable
BBCEC permeability to sucrose unchanged
Protein is transported intact

Exhibit E

Distribution of p97 into mouse brain during *in situ* perfusion

(10 nM proteins, 10 minutes)

Negative Control — **Parenchymal V_d for ^{14}C-inulin is 17 µL/g**

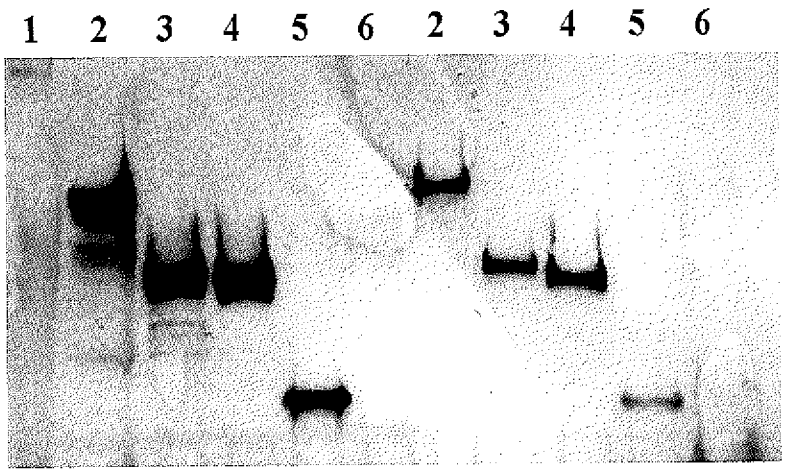
Positive Control — **Parenchymal V_d for ^{125}I-hTf is 24 µL/g**

Parenchymal V_d for ^{125}I-p97 is 172 µL/g

Beliveau et al.
Journal of Neurochemistry, accepted for publication

Exhibit F

Data on p97-idu fusions from transient transfection 3/1/02



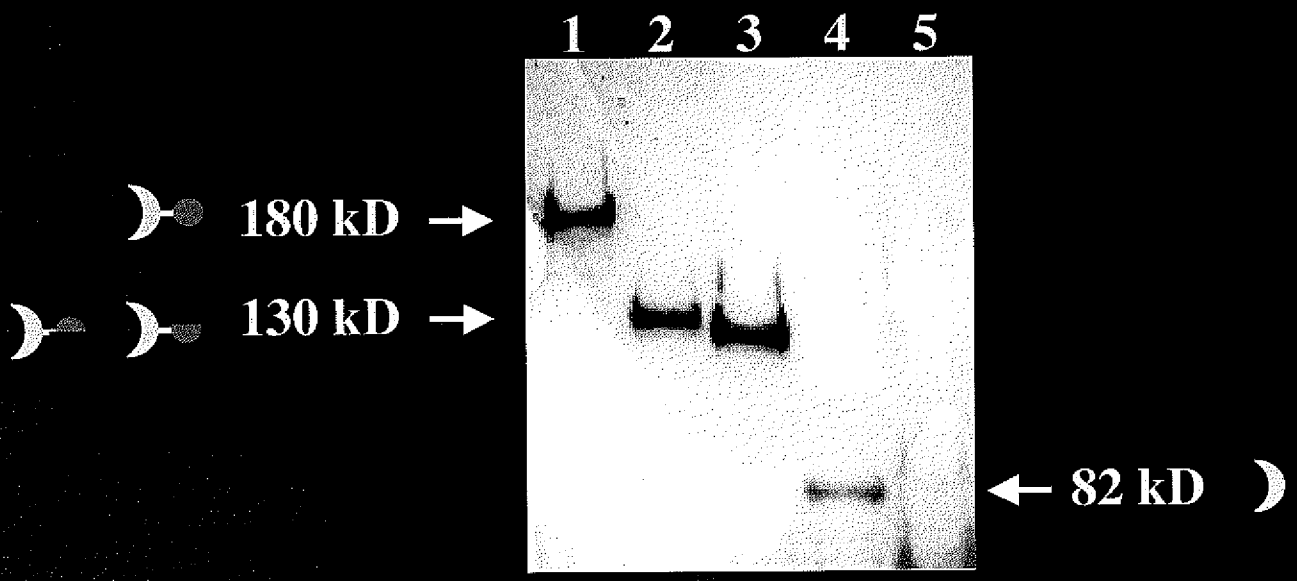
Invitrogen NuPage 3-8% Tris-Acetate Gel (reducing)
probed with anti-Idu antibody

lane		protein	vector	secreted units/cell
1	MW Markers			
2	p97N Idu	p97-idu	pC3B	12
3	Idu	p97C-idu	pC3B	8
4	p97N Idu	p97N-idu	pC3B	22
5	Idu	idu	pcDNA3.1	6
6		empty vector	pcDNA3.1	0

Exhibit G

Expression of p97-iduronidase fusions

Iduronidase Western Blot

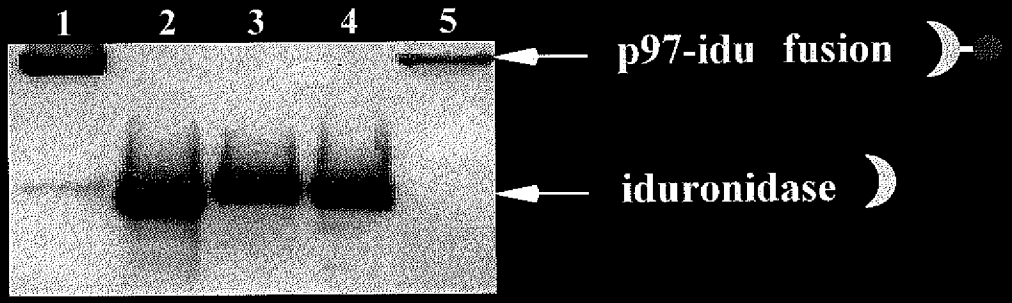


1. full-length p97-iduronidase fusion
2. p97 N-terminal lobe-iduronidase fusion
3. p97 C-terminal lobe-iduronidase fusion
4. iduronidase
5. empty vector

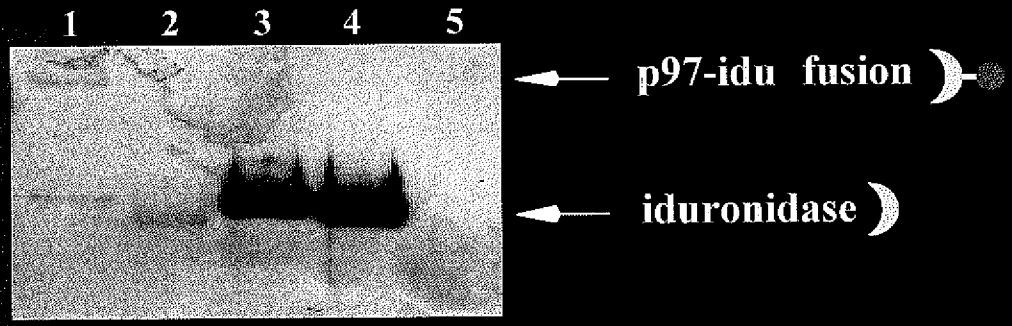
Exhibit H

Phosphorylation Status of the p97-iduronidase Fusion

Iduronidase Western Blot



Mannose 6-phosphate Blot



1 μg of each protein per lane

1. p97-iduronidase fusion
2. dephosphorylated iduronidase control
3. phosphorylated iduronidase control
4. same as 3
5. concentrated p97-iduronidase harvest medium

Exhibit I

Uptake of p97 and iduronidase into HCN-2 neuronal cells (2 hour incubation, 60 μg/mL proteins)

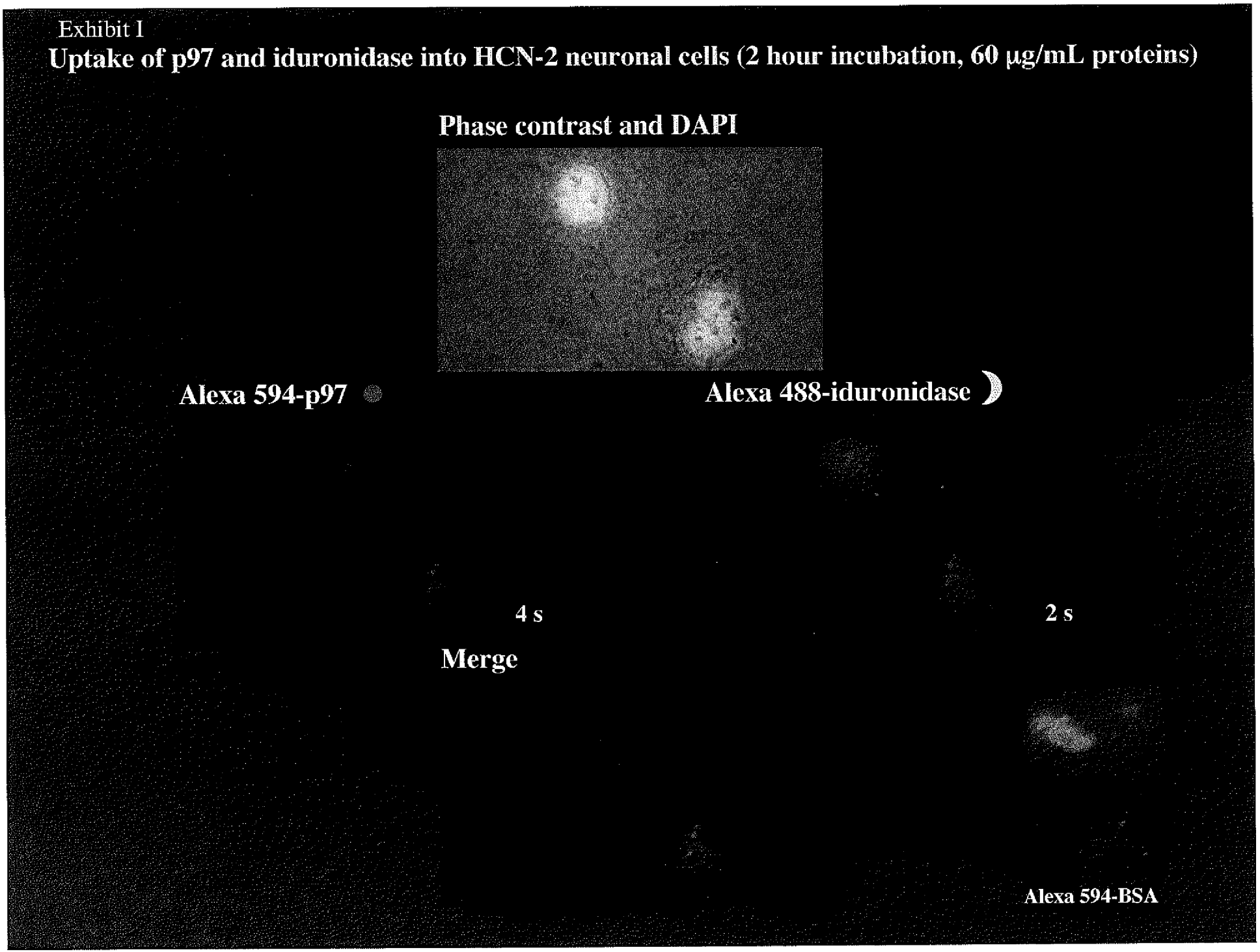
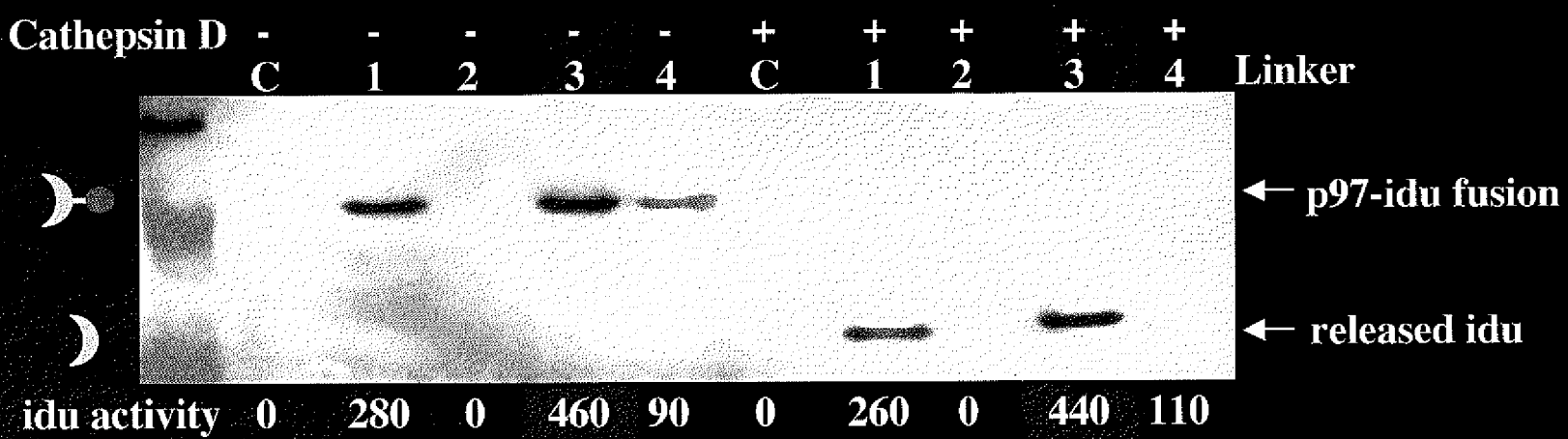


Exhibit J

Cathepsin D proteolysis of p97-iduronidase fusions (37°C, 1 hour)

Iduronidase Western Blot



p97 Western Blot

